PATENT
Docket No. 506562000200

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Chase Trombella

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In the application of:

Warren K. HOEFFLER

Serial No.: 09/622,703

Filing Date: August 21, 2000

For: METHOD FOR DETERMINING TRANSCRIPTION FACTOR ACTIVITY AND ITS TECHNICAL USES

Examiner: A. K. Chakrabarti

Group Art Unit: 1634

BRIEF ON APPEAL

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is an Appeal from the final rejection of claims 1-14 in the above-referenced application. In accordance with 37 C.F.R. § 1.192, this Brief, along with the Appendix, is filed in triplicate. The required fee has been previously submitted.

I. Real Party in Interest

XGene Corporation, a California corporation, with a principal place of business in Burlingame, California, is the real party in interest.

II. Related Appeals and Interferences

There are no known related appeals or interferences.

III. Status of Claims

Claims 1-14 are pending in the present application, and are reproduced in Appendix A attached hereto.

Claims 1-2, 4-8, 10, and 13 are rejected under 35 U.S.C.§102(b) as being anticipated by Gansz et al. (Molecular and General Genetics, (1991), Vol. 225, pages 427-434).

Claims 1-2, 4-10, and 13-14 are rejected under 35 U.S.C.§103(a) over Gansz et al. (Molecular and General Genetics, (1991), Vol. 225, pages 427-424) in view of Mirzabekov et al. (US 5,851,772).

Claims 1-8 and 10-13 are rejected under 35 U.S.C.§103(a) over Gansz et al. (Molecular and General Genetics, (1991), Vol. 225, pages 427-434) in view of Hodgson et al. (US 5,854,020).

IV. Status of Amendments

A reply filed August 6, 2002 was submitted after final rejection, but deemed not to place the application in condition for allowance. No amendments to the claims were presented in the August 6, 2002 reply.

V. Summary of Inventions

The presently claimed inventions relate to Applicant's discovery that certain transcription factors catalyze transcription by the creation of single-stranded, and in some cases double-

stranded, nicks in the DNA strands of a gene template. (See generally page 3, lines 8-11.) As set forth in the specification, the nick in the DNA serves as an entry site for an RNA polymerase complex. The complex migrates down the DNA to the transcription start site where transcription is initiated.

The presently claimed inventions are particularly drawn to methods of detecting transcription activity requiring the claimed step of "detecting the presence or absence of a nick in a DNA molecule," wherein the presence of a nick in a DNA molecule is indicative of transcription activity (page 3, lines 11-13; page 11, lines 28-31). The claimed methods present a powerful new way to analyze for transcription activity. Independent claims 1 and 10 are representative and are reproduced below for convenience:

> 1. A method of detecting transcription activity comprising detecting the presence or absence of a nick in a DNA molecule, wherein the presence of a nick in the DNA molecule indicates transcription activity.
>
> 10. A method of detecting transcription activity comprising the steps of :
> a) providing a DNA template comprising at least one binding region for a transcription factor;
> b) contacting the DNA template with at least one transcription factor; and
> c) detecting the presence or absence of a nick in the DNA template, wherein the presence of a nick in the DNA template indicates transcription activity.

(See page 3, lines 11-13; page 11, lines 28-31.) Various techniques can be employed to detect the presence or absence of the DNA nicks, including adapting otherwise known techniques, such as, electrophoretic gels, primer extension reactions, PCR amplification, DNA sequencing assays, and protein binding assays, to detect the presence or absence of DNA nicks. (See generally page 18, lines 18-25.) Dependent claims from claims 1 or 10 above include methods wherein the nick is detected by an electrophoretic gel (claim 2) (page 19, lines 4 and following), a S1 nuclease assay (claim 3) (page 24, lines 12 and following), primer extension reaction (claim 4) (page 25, lines 10 and following), PCR amplification reaction (claim 5) (page

30, lines 2 and following), DNA sequencing assay (claim 6) (page 32, lines 4 and following), and protein binding assay (claim 7) (page 21, lines 4 and following). Additional dependent claims from claims 1 or 10 are directed to methods wherein the DNA is affixed to a matrix (claims 13 and 14) (page 35, lines 24 and following), the transcription factor is in a nuclear cell extract (claim 10) (see e.g. page 12, line 6 through page 14, line 24) , and the DNA template is inserted into a viral or plasmid vector and introduced into a cell (claim 12) (see e.g. page 14, line 26 through page 16, line 28).

VI. Issues

(1) Whether Gansz, et al. (Molecular and General Genetics, (1991), Vol. 225, 427-434), which teaches a bacterial phage (virus) binding protein, DsbA, that nicks a DNA molecule, but which does not appreciate DNA nicking as predictive of transcription activity, anticipates the claimed methods directed to the detection of transcription activity by detecting the presence or absence of a nick in a DNA molecule.

(2) Whether Gansz, et al. (Molecular and General Genetics, (1991), Vol. 225, 427-434), which teaches a bacterial phage (virus) binding protein, DsbA, that nicks a DNA molecule, but which does not appreciate DNA nicking as predictive of transcription activity, in combination with U.S. Patent No. 5,851,772 (Mirzabekov, et al.), which teaches DNA affixed to a chip, renders obvious the claimed methods directed to the detection of transcription activity by detecting the presence or absence of a nick in a DNA molecule.

(3) Whether Gansz, et al. (Molecular and General Genetics, (1991), Vol. 225, 427-434), which teaches a bacterial phage (virus) binding protein, DsbA, that nicks a DNA molecule, but which does not appreciate DNA nicking as predictive of transcription activity, in combination with U.S. Patent No. 5,854,020 (Hodgson, et al.), which teaches a method of transcription initiation site determination by S1 nuclease activity, renders obvious the claimed

methods directed to the detection of transcription activity by detecting the presence or absence of a nick in a DNA molecule.

VII. Grouping of Claims

Claims 1-14 stand or fall together.

VIII. Argument

Rejection under 35 U.S.C. §102(b)

Claims 1-2, 4-8, and 10-13 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Gansz, et al. Molecular and General Genetics, (1991), Vol. 225, 427-434 (hereinafter "Gansz, et al.") The rejection is in error. Contrary to the Examiner's position, Gansz, et al. does not in any way teach the claimed methods of detecting transcription activity that require the step of detecting the presence or absence of a nick in DNA.

A. The Examiner has mischaracterized the teachings of Gansz, et al.

In the Final Office Action of June 6, 2002, sustaining the above rejection (hereinafter "Final Action"), the Examiner characterized Gansz, et al., as follows:

> Gansz et al teach a method of detecting transcription activity (Summary) comprising the steps of:
> a) providing a DNA template comprising at least one binding region for a transcription factor (Page 428, column 1, Materials and Methods Section, DNA isolation subsection);
> b) contacting the DNA template with at least one transcription factor (Figures 1 and 2 and Materials and Methods Section, Gel-retardation assay subsection);
> c) detecting the presence or absence of a nick in the DNA template, wherein the presence of a nick in the DNA template indicates transcription

activity (Summary, lines 11-12 and Results and Discussion section, The DsbA protein induces DNA nicking subsection and Figures 2-5).

Gansz et al teach a method wherein the presence or absence of a nick in a DNA molecule is measured by determining the change in electrophoretic mobility of nicked DNA on an electrophoretic gel by a DNA sequencing assay (Figure 5 and Materials and Methods Section, DNAse I foot printing subsection).

Gansz et al teach a method wherein the presence or absence of a nick in a DNA molecule is determined by a primer extension, polymerase chain reaction and amplification reaction (Materials and Methods Section, DNA sequencing subsection).

Gansz et al teach a method wherein the presence or absence of a nick in a DNA molecule is determined by a protein binding assay (Figure 2 and Results and Discussion section, Gel Retardation Assay subsection).

Gansz et al teach a method wherein the DNA is affixed to a gel matrix (Figures 2-5 and Materials and Methods Section, In vitro transcription assays subsection).

(Final Action, pages 2-3.) As previously argued by Applicant and as further addressed herein, the above grossly mischaracterizes the teachings of the Gansz, et al. reference. Gansz, et al. simply does not teach or even suggest methods of detecting transcription activity that require the step of detecting the presence or absence of a nick in DNA as is claimed.

With respect to the Examiner's more specific characterizations of the reference, Applicant notes that each specific citation the Examiner makes to the Gansz, et al. fails in all respects to support the Examiner's corresponding proposition, as is further detailed herein.

(1) Summary, "The DsbA protein induces nicking" subsection, Figures 2-5

Beginning first with the Examiner's proposition that the Gansz, et al. reference allegedly teaches:

[A] method of detecting transcription activity (Summary) comprising the steps of:
. . .

> c) detecting the presence or absence of a nick in the DNA template, wherein the presence of a nick in the DNA template indicates transcription activity (Summary, lines 11-12 and Results and Discussion section, The DsbA protein induces DNA nicking subsection and Figures 2-5).

(Final Action, page 2.) Applicant submits that a careful review of the cited sections reveals that none of these sections provide any support whatsoever for the proposition that Gansz, et al. teaches a "method of detecting transcription activity" that involves the step of "detecting the presence or absence of a nick in the DNA template."

The Summary itself teaches no such method. In particular, the cited lines 11-12 of the Summary read as follows: "[A]t the sites of binding the protein [DsbA] introduces nicks in double-stranded DNA." (Gansz, et al., page 427, column 1, Summary, lines 11-12.) This is an observation; it is not a teaching of a *method* of detecting transcription activity that relies upon detecting the presence or absence of a nick in the DNA template. Further review of the Summary as a whole reveals this to be the case. The entire Summary is reproduced below.

> Gene product 33 of phage T4 is known to be essential in late transcription Upstream from gene *33* and overlapping its 5' terminal sequence by 20 bp, we identified an open reading frame coding for a binding protein for double-stranded DNA (DsbA). Gene product DsbA is composed of 89 amino acid residues wit a M_r of 10376 kDa. We purified this protein to homogeneity from over-expressing cells. Gel retardation assays reveal that it binds to DNA and footprint analyses disclose that it interacts preferentially with T4 late promoter regions. At the sites of binding the protein introduces nicks in double-stranded DNA. In vitro transcription assays performed with T4 late modified RNA polymerase on restriction fragments harbouring a T4 late promoter region prove that gene product DsbA enhances transcription from these promoter regions in the presence of gene product 33. Gene *dsbA* is distinct from gene *das* which maps close to this genomic region.

(Gansz, et al., page 427, column 1, Summary.) Thus, the Summary effectively teaches (a) that the authors have identified a phage T4 DNA binding protein, which they refer to as DsbA, (b) that they have determined that it binds to DNA and interacts preferentially with T4 late promoter

regions and that at the sites of binding it introduces nicks in the DNA, and (c) that it *enhances transcription* from T4 late promoter regions *in the presence of a second protein, gene product 33*, which is known to be essential to T4 late transcription. (Id.) That is to say, the Summary teaches that the authors have identified a T4 DNA binding protein, DbsA, that binds to T4 late promoter regions and enhances T4 late transcription in the presence of gene product 33, and which also introduces nicks in the DNA. But that is all. There is no indication whatsoever in the Summary that DNA nicking is predictive of transcription, or in particular of a "method of determining transcription activity" involving the step of "detecting the presence or absence of DNA nicking" as is stated by the Examiner. Such a teaching is simply not present in the Summary, either explicitly or implicitly.

Analysis of the Results and Discussion subsection entitled "The DsbA protein induces DNA nicking" likewise leads to the same conclusion. In this subsection, the authors describe complexing the DsbA protein with plasmids containing T4 late promoter regions. As the authors note, "[t]he protein nicks both plasmids." (Id., page 432, column 2, Fig. 5.) In an experiment that resembled the DNase I protection analysis experiments (i.e., so-called "footprinting" experiments), where the DbsA protein was allowed to bind a T4 late promoter plasmid but where DNase I treatment was omitted, the authors report separating the reaction products and observing a "minor cleavage site" at the end of the region protected by the protein and a "major cleavage site" eight bases downstream. (Id., page 432, column 2 through page 433, column 1.) However, of critical significance is the fact that the authors had no idea what to make of this observed DNA cleavage. Rather, the authors explicitly state the following:

> Surprisingly, the nicks are observed on the template strand and must separate the promoter from the downstream structural genes. *At present we have no explanation for this result.* It should be noted that the protein exhibits a strong adenosine triphosphatase activity. Therefore, the DNA cleavage observed might

> be an artificial reaction, occurring only in the absence of certain cofactors or additional reaction partners. Alternatively, the protein might remain attached to the cleavage site, either anchoring both ends and leaving the DNA strand formally intact, or occupying e.g. the free 3-OH terminus. Such a complex might possibly represent an activated template, facilitating DNA swiveling and promoter opening or the binding of late modified polymerase to a promoter marker protein and effective late RNA synthesis.

(Id., at page 433, column 1, emphasis added.) In other words, the authors have no idea what implications, if any, can be drawn from the observed nicking phenomena. Also of importance is the fact that these experiments were performed under conditions that would not allow for actual transcription to take place, (i.e. no additional necessary transcription factors, polymerases, nucleoside bases, etc.). How then can this support a conclusion that Gansz, et al. teaches methods of determining transcription activity that involve "detecting the presence or absence of DNA nicking" as stated by the Examiner? The answer is it cannot.

Finally, the Examiner's reliance on Figs. 2-5 as allegedly teaching a "method of determining transcription activity" that relies on "detecting the presence or absence of DNA nicking" is equally misplaced. Each figure represents results from experiments aimed at determining characteristics of the DsbA protein. But none of the figures show assay methods for determining transcription activity that relies on "detecting the presence or absence of DNA nicking" as is stated by the Examiner. Each Figure will now be discussed in turn.

Figure 2 shows gel retardation analysis of DNA fragments, some of them carrying T4 early and/or late promoter regions, complexed with DsbA protein. Only those fragments carrying T4 late promoter regions were resistant to competition with λ DNA and were retarded on the gels. (See Id., page 431, column 1.) In other words, the gel retardation assays of Figure 2 confirm that DsbA binds to T4 late promoter regions, but do not in any way demonstrate a

"method of determining transcription activity" that involves "detecting the presence or absence of DNA nicking" as is stated by the Examiner.

Figure 3 shows DNase I footprint analyses of T4 DNA fragments containing late promoter sequences. Specifically, the fragments were incubated with the DsbA protein and exposed to DNase I hydrolysis. The authors performed these experiments to determine more precisely the region of protein-DNA interaction. (Id., page 432, column 1.) In other words, the footprint analyses of Figure 3 show where DsbA binds to T4 DNA, but do not in any way demonstrate a "method of determining transcription activity" that involves "detecting the presence or absence of DNA nicking" as is stated by the Examiner.

Figure 4 shows the effect of DsbA on in vitro run-off transcription. T4 DNA fragments carrying the T4 late promoter were incubated with T4 late polymerase supplemented with gene products 55 and 33 together with the necessary ribonucleoside bases for transcription. The addition of stoichiometric amounts of DsbA to the system stimulated transcription, resulting in two distinct transcripts of 300 and 305 bases. (Id., page 432, columns 1-2.) While these assays do detect transcription activity, it is important to note that the transcription activity was measured by resolving the resultant transcripts on a gel, and not by "detecting the presence or absence of DNA nicking" as is stated by the Examiner. That is, the method detects the transcript product, not a DNA nick. Based on these results of these assays, the authors conclude the following:

> The results strongly suggest that the stimulation of transcription starting at the late promoter region is brought about by an interaction between gene products 33 and DsbA. Gp33 acts as a mediator between DsbA and late modified RNA polymerase.

(Id.) Thus the authors are recognizing that DsbA plays a role in late T4 transcription, but this conclusion in no way portends a "method of determining transcription activity" that relies on "detecting the presence or absence of DNA nicking" as is stated by the Examiner.

Figure 5 shows that DsbA catalyzes nicking of double-stranded vector DNA carrying the late T4 promoter region. The results of Figure 5 form the basis of discussion in the subsection entitled "The DsbA protein induces DNA nicking." As noted above, nothing in this subsection can be construed as teaching a "method of determining transcription activity" that relies on "detecting the presence or absence of DNA nicking" as is stated by the Examiner. Figure 5 itself shows the results of a method, specifically gel electrophoresis, for resolving nicked plasmids, under conditions that would not allow for actual transcription. But this does not equate into a showing of a method of detecting transcription activity, as is stated by the Examiner.

(2) Figure 5, "DNase I foot printing" subsection

Next, the Examiner states that

> Gansz et al. teach a method wherein the presence or absence of a nick in a DNA molecule is measured by determining the change in electrophoretic mobility of nicked DNA on an electrophoretic gel by a DNA sequencing assay (Figure 5 and Materials and Methods Section, DNAse I foot printing subsection).

(Final Action, page 3.) As noted above, Figure 5 itself shows the results of a gel electrophoresis resolving nicked plasmids prepared under conditions that would not allow for transcription. It may be assumed that the resolution of the nicked plasmids is the result of a change in electrophoretic mobility of the nicked plasmid as compared to the intact plasmid. However, as also noted, Figure 5 itself does not teach a method of determining transcription activity.

The Materials and Methods subsection entitled "DNAse I foot printing" describes particular gel electrophoresis conditions for the DNAse I footprinting analysis experiments. (Gansz, et al., page 429.) The results are depicted in Figure 3. (Id. at page 431.) As noted above, and as further detailed in the Results and Discussion subsection entitled "DNAse I protection analysis," (Id. at p. 432) the footprint analyses experiments show where DsbA binds to

T4 DNA, but do not in any way demonstrate a method of determining transcription activity, let alone one that relies on "detecting the presence or absence of DNA nicking."

(3) "DNA sequencing" subsection

Next, the Examiner states that

> Gansz et al. teach a method wherein the presence or absence of a nick in a DNA molecule is determined by a primer extension, polymerase chain reaction and amplification reaction (Materials and Methods Section, DNA sequencing subsection).

(Final Action, page 3.) The cited subsection teaches nothing of the kind. Rather this subsection describes a DNA sequencing technique used to sequence T4 mutant DNA. (Gansz, et al., page 428.) Specifically, DNA was digested with a restriction enzyme, purified restriction fragments were hybridized to primers, and the primers were extended by a polymerase reaction. In no way can this subsection can be construed as teaching "a method wherein the presence or absence of a nick in a DNA molecule is determined by a primer extension, polymerase chain reaction and amplification reaction" as is stated by the Examiner. The mere act of sequencing T4 mutant DNA as described does not detect the presence or absence of DNA nicks.

(4) Figure 2, "Gel Retardation Assay" subsection

Next, the Examiner states that

> Gansz et al. teach a method wherein the presence or absence of a nick in a DNA molecule is determined by a protein binding assay (Figure 2 and Results and Discussion section, Gel Retardation Assay subsection).

(Final Action, page 3.) Again, the cited figure and subsection teach no such thing. As already noted, and as further detailed in the Gel Retardation Assay subsection, Figure 2 shows gel retardation analysis of DNA fragments, some of them carrying T4 early and/or late promoter

regions, complexed with DsbA protein. (Gansz, et al., pages 430-431.) Thus, the gel retardation assays described in the subsection and shown in Figure 2 confirm that DsbA binds to T4 late promoter regions. But this does not in any way demonstrate a "method of wherein the presence or absence of a nick in a DNA molecule is detected by a protein binding assay" as is stated by the Examiner.

(5) Figures 2-5, "In vitro transcription assays" subsection

Finally, the Examiner states that

> Gansz et al. teach a method wherein the DNA molecule is affixed to a gel matrix (Figures 2-5 and Materials and Methods Section, In vitro transcription assays subsection).

(Final Action, page 3.) Applicants have little quarrel here. Figures 2, 3 and 5 do show DNA gels, although Figure 4 and the cited subsection detail resolution of RNA transcripts, not DNA, on a gel. (Gansz, et al., pages 430-433.) However, the specific teaching of affixing DNA to a gel matrix is ultimately irrelevant to the present case, as such teaching does not in any way demonstrate a method of determining transcription activity, let alone one that relies on "detecting the presence or absence of DNA nicking."

B. Comparison of Gansz et al. to claimed methods

From the above, it can be readily seen that the Examiner's interpretation of Gansz, et al. is in error. Gansz, et al. discloses a specific bacteriophage T4 binding protein, DsbA, that binds to T4 late promoter regions, and further discloses that this DsbA protein introduces nicks in the T4 DNA. However, the only *method* of determining transcription activity taught by Gansz, et al. is the conventional method of assaying for run-off transcripts. (Gansz, et al., page 432, "Transcription Experiments" and Figure 4.) Specifically, restriction fragments carrying T4 late promoter were incubated with T4 late RNA polymerase, gene products 55 and 33, the DsbA

binding protein, and the four ribonucleoside-5'-triphosphates (including ^{32}P-labeled UTP). Run-off transcripts of approximately 300 and 305 bases were observed and resolved by gel electrophoresis (see Fig. 4). This is a classic example of determining transcription activity by assaying for the transcription *product*, i.e., the transcript itself. However, it is not a method of determining transcription activity that requires the step of "detecting the presence or absence of DNA nicking."

(1) Each and every element of claimed methods not taught by Gansz, et al.

It is well settled that for a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim. *Akzo N.V. v. United States Int'l Trade Comm'n*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987). Further, the disclosure of each and every element must be "with sufficient clarity to prove its existence" in the prior art reference. *Motorola, Inc. v. Interdigital Tech. Corp.* , 43 USPQ2d 1481, 1490 (Fed. Cir. 1997); *see also In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("[T]he [prior art] reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it." (citations omitted)). Thus, while the disclosure requirement presupposes the knowledge of one of ordinary skill in the art, such "presumed knowledge does not grant a license *to read into the prior art references teaching that are not there.*" *Motorola v. Interdigital Tech. Corp.*, 43 USPQ2d at 1490 (emphasis added).

Applying this standard to independent claims 1 and 10, it can be readily appreciated that Gansz, et al. does not disclose a method of detecting transcription activity that requires the step of "detecting the presence or absence of DNA nicking" as is required by both independent claims 1 and 10. The Examiner's mischaracterization of Gansz, et. al. as somehow including methods of detecting transcription activity requiring the claimed step is reading into Gansz, et al. teachings which simply are not there, a practice forbidden by *Motorola*.

(2) Claimed methods not inherent in Gansz, et al.

The Examiner also appears to support the rejection of the claimed methods on the erroneous basis of inherent properties of the Gansz, et al. DsbA binding protein (a compound). Specifically, in replying to Applicant's prior arguments, the Examiner states the following:

> [T]he property of transcription as a result of nicking is inherently present in this chemically and structurally identical molecule,

presumably referring to the DsbA binding protein. (Final Action, page 7.) But, as further discussed herein, the inherent properties of a compound alone are not sufficient to render method claims unpatentable. Thus any such rationale for supporting the rejection is misplaced.

Of course, a prior art reference can anticipate a claim without expressly disclosing each and every limitation of the claim, provided those claim limitations not expressly disclosed are otherwise inherently found within the reference. *See e.g., Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 51 USPQ2d 1943 (Fed. Cir. 1999), *Continential Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991). It is well settled that the discovery of a previously unknown advantage of a known compound does not render the compound itself patentable anew. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Similarly, newly discovered results of known processes directed to the same purpose are likewise not newly patentable. *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978); *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 6289, 633, 2 USPQ2d 1051, 1054 (Fed. Cir. 1987). However, new uses of known processes can be patentable. *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1376, 58 USPQ2d 1508, 1514 (Fed. Cir. 2002). And, it has never been the case that a known compound per se renders new methods of use unpatentable. *See In re Woodruff*, 919 F.2d at 1578, 16 USPQ2d at 1936 (citing cases where inventions to a new use of an old or obvious compound were held patentable). Rather, inherency requires a determination of whether the inherent characteristic relied upon is necessarily present in what is described in the relied upon reference, and whether it would be so

recognized by persons of ordinary skill in the art. *Continental Can,* 948 F.2d at 1268, 20 USPQ2d at 1749.

In the present case, the Gansz, et al. reference fails on this account. As already discussed in detail, Gansz, et al. teaches a transcription factor, DbsA, that nicks T4 DNA. But Gansz, et al. does not teach methods of detecting transcription activity that require detecting the presence or absence of a nick in DNA, as is claimed. Further, Gansz, et al. in no way appreciates that nicking of DNA is predictive of transcription activity, therefore Gansz, et al. cannot be relied upon for even suggesting the claimed methods.

C. Examiner's prior response to Applicant's arguments inapposite

In replying to Applicant's prior arguments, the Examiner also takes other positions that are wholly inapposite to the issues presented herein, specifically, positions with respect to (a) the role of preferred embodiments in prior art references, and (b) scope of claim interpretation during prosecution. However, these positions have no bearing on the present case.

With respect to the role of preferred embodiments in prior art references, the Examiner at the outset mistakenly states the following:

> Applicant argues that because Gansz has a preferred embodiment of speculation, Gansz is limited to the preferred embodiment.

(Final Action, page 7.) Applicant, however, has made no such argument. Indeed, Applicant is at a loss as to how "speculation" could ever be a preferred embodiment.

The Examiner then proceeds to set forth the following principles: (1) that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments, citing *In re Susi*, 169 USPQ 423 (CCPA 1971), and (2) that a reference may be relied upon for all that it would reasonably suggest to one skilled in the art, including non preferred embodiments, citing *Merck & Co. v. Biocraft Laboratories*, 10 USPQ2d 1843 (Fed. Cir. 1989). (Final Action, page 7.) Applicant does not take issue with either point of law, and has not argued otherwise, but the application of these principles to the

present case is moot. Gansz, et al. does not teach any embodiment of the claimed method -- preferred, non-preferred or otherwise.

Next, the Examiner states that claims must be given their broadest reasonable interpretation during prosecution, citing *MPEP* § 211 and *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969). Again, Applicant does not take issue with this point of law, but its application to the present case is likewise irrelevant. Applicant has not argued that the Examiner has misinterpreted the claims, but rather that the prior art fails to anticipate the claims.

Given all of the above, Gansz et al. cannot be considered to anticipate either independent claim 1 or 10, or by extension any claims depending therefrom.

Rejections under 35 U.S.C. §103

A. Rejection over Gansz, et al. in view of Mirzabekov

Claims 1-2 and 4-14 stand rejected over 35 U.S.C. § 103 as being obvious over Gansz, et al. in view of U.S. Patent No. 5,851,772 (Mirzabekov, et al.). The rejection is in error.

Mirazabekov is directed to methods for enriching specific DNA sequencing using oligonucleotide microchips, but does not speak at all to methods of detecting transcription activity. Mirazabekov is particularly relied upon for teaching DNA affixed to a biological chip. (Final Action, page 4.) In making the rejection, the Examiner states:

> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the DNA affixed to a biological chip of Mirzabekov et al. in the method of detecting transcription activity of a DNA molecule of Gansz et al.

(Id.) A critical requirement of any *prima facie* case of obviousness, however, is that the prior art references when combined teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *MPEP* § 2142. The deficiencies of Gansz, et al. as the

primary reference has been discussed above. To repeat, Gansz, et al. neither teaches nor suggests methods of detecting transcription activity that require the step of "detecting the presence or absence of a nick in the DNA" as is claimed. The combination of Gansz, et al. with the DNA chips of Mirzabekov does nothing to alleviate these deficiencies. That is, there is nothing in Mirzabekov, alone or in combination with Gansz, et al., that teaches or suggests this missing step. Therefore, the combination of Gansz, et al. and Mirzabekov cannot render independent claims 1 and 10 *prima facie* obvious, or any claim depending therefrom.

In replying to Applicant's prior arguments, the Examiner takes further positions under 35 U.S.C. §103 that, upon closer analysis, are ultimately moot or incorrect. In particular, the Examiner first states that one cannot show nonobviousness by attacking the references individually where the rejections are based on combinations of references. (Final Action, page 8, citing *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981; *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). Applicant agrees. However, Applicant has not attacked the references individually, but rather demonstrated that the combination of references does not achieve the claimed methods. Next the Examiner states that Applicant's prior argument regarding a lack of motivation to combine references is not persuasive. (Id. at page 8, notably discussing only the Hodgson, et al. reference discussed below, and then concluding "This logic is applicable to the other 103(a) rejection as well.") Applicant notes that it is the suggestion or motivation to combine and/or modify the prior art references to make the claimed invention that is crucial. As discussed, neither Gansz, et al. nor Mirzabekov, alone or in combination, teaches nor suggests the claimed methods of detecting transcription activity that require the step of "detecting the presence or absence of a nick in the DNA."

Finally, the Examiner argues there is no evidence of record submitted by Applicant "demonstrating the absence of a reasonable expectation of success." (Final Action, page 10.) In particular, the Examiner states the following:

> There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Gansz reference of the

enabling methodology, the suggestion to modify the prior art, and evidence that a number different nicks in the DNA of T4 bacteriophage were actually experimentally studied and found to be functional to enhance transcription (Abstract and Page 428, column 1, lines 2-7). This evidence of functionality trumps the attorney arguments, which argues that Gansz reference is an invitation to research, since Gansz steps beyond research and shows the functional product.

(Id.) With respect to this line of reasoning, Applicants note the following. First, evidence of the absence of reasonable expectation of success is not required where, as here, the Examiner has failed at the outset to present a *prima facie* case of obviousness. Second, contrary to the Examiner's contention, Gansz et al. does not provide "the enabling methodology" and "the suggestion to modify the prior art" to achieve the claimed methods. Rather, as discussed extensively above, Gansz, et al. contains no teaching, suggestion, or faintest hint of the claimed methods of detecting transcription activity that require the step of "detecting the presence or absence of a nick in the DNA." Third, the cited portions of Gansz, et al. do not support the Examiner's position that Gansz, et al. discloses that "*evidence* that...*nicks* in the DNA of T4 bacteriophage *were actually studied and found to be functional* to enhance transcription." (Id., emphasis added.) Instead, as previously discussed, the authors noted the nicking phenomena (Gansz, et al., Abstract), speculated that nicks "*might* contribute to activation of the template for late transcription," (Id., at page 428, column 1, lines 2-7.), but ultimately had *no explanation* for the nicking phenomena (Id., at page 433, column 1). Therefore, Gansz, et al. does not at all establish that nicks are functional to enhance transcription. Finally, Applicant is uncertain as to what the Examiner is referring to as a "functional product" of Gansz, et al. But if the Examiner is referring here to the Gansz, et al. DbsA binding protein, as noted earlier, an unknown and unappreciated inherent property of the protein does not render the claimed methods unpatentable.

B. Rejection over Gansz, et al. in view of Hodgson

Claims 1-8 and 10-13 stand rejected over 35 U.S.C. § 103 as being obvious over Gansz, et al. in view of Hodgson, et al. (U.S. Patent No. 5,854,020). The rejection is in error.

Hodgson is directed to polynucleotides and polypeptides in the family of the ResD response regulatory protein from *B.subtilis*. Hodgson is particularly relied upon for teaching a methods where a transcription initiation site is determined by S1 nuclease activity, where a transcription factor is in a nuclear cell extract, and where a DNA template is inserted into a viral or plasmid vector and introduced in a cell. (Final Action, pages 5-6.) In making the rejection, the Examiner states:

> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the transcription initiation site determination by S1 nuclease assay and viral or plasmid vector as well as using the transcription factor from a nuclear cell extract of Hodgson et al. in the method of detecting transcription activity of a DNA molecule of Gansz et al.

(Id. at page 6.) Again, a *prima facie* case of obviousness requires the prior art references when combined teach or suggest all the claim limitations. The deficiencies of Gansz, et al. as the primary reference has been discussed above, namely, Gansz, et al. neither teaches nor suggests methods of detecting transcription activity that require the step of "detecting the presence or absence of a nick in the DNA." The combination of Gansz, et al. with the S1 nuclease assay, viral or plasmid vectors, and transcription factors in nuclear cell extracts of Hodgson, et al. likewise does nothing to alleviate these deficiencies. There is nothing in Hodgson, alone or in combination with Gansz, et al., that teaches or suggests this missing step. Hodgson, et al. teaches using a S1 nuclease assay to identify a transcription initiation promoter sequence site, i.e. to map the site but not to detect the presence or absence of DNA nicks. (Hodgson, et al., column 5, lines 21-25.) Therefore, the combination of Gansz, et al. and Hodgson, et al. cannot render independent claims 1 and 10 *prima facie* obvious, or any claim depending therefrom.

In replying to Applicant's prior arguments, the Examiner also takes the same additional positions under 35 U.S.C. §103 discussed above with respect to the rejection under Gansz, et al.

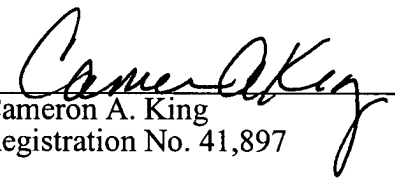
in view of Mirzabekov. Applicant's above comments with respect thereto are equally applicable here.

CONCLUSION

For the foregoing reasons, Appellant believes the Examiner's rejections of claims 1-14 are erroneous and that the claims are patentable. Reversal of the rejections is therefore respectfully requested.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to Deposit Account No. 03-1952.

Respectfully submitted,

Dated: December 18, 2002 By: 

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Attached: Appendix A
(copy of claims involved in the Appeal)

APPENDIX A

1. A method of detecting transcription activity comprising detecting the presence or absence of a nick in a DNA molecule, wherein the presence of a nick in the DNA molecule indicates transcription activity.

2. The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is measured by determining the change in electrophoretic mobility of nicked DNA on an electrophoretic gel.

3. The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is determined by a SI nuclease assay.

4. The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is determined by a primer extension reaction.

5. The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is determined by a polymerase chain reaction amplification reaction.

6. The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is determined by a DNA sequencing assay.

7. The method of claim 1 wherein the presence or absence of a nick in a DNA molecule is determined by a protein binding assay.

8. The method of claim 1 wherein the DNA is affixed to a matrix.

9. The method of claim 8 wherein the matrix is a biological chip.

10. A method of detecting transcription activity comprising the steps of :

a) providing a DNA template comprising at least one binding region for a transcription factor;

b) contacting the DNA template with at least one transcription factor; and

c) detecting the presence or absence of a nick in the DNA template, wherein the presence of a nick in the DNA template indicates transcription activity.

11. The method of claim 10, wherein the transcription factor is in a nuclear cell extract.

12. The method of claim 10, wherein the DNA template is inserted into a viral or plasmid vector and introduced into a cell.

13. The method of claim 10, wherein the DNA template is fixed to a matrix.

14. The method of claim 13, wherein the matrix is a biological chip.